REMARKS/ARGUMENTS

Claims 1-33 have been cancelled through previously submitted Amendment. Claim 34-51 are pending. No amendment is made to any of the pending claims. Reconsideration of the present application in view of the following remarks is respectfully solicited.

In the final Office Action dated January 28, 2010, the Examiner maintains the rejection of claims 34-51. Applicants still believe that the arguments they submitted previously on September 29, 2009 have merit, and therefore incorporate the arguments of September 29, 2009 in its entirety in this response. The following will focus on the Examiner's new comments

I. Rejection of claims 34-51 as being obvious under 35 U.S.C. §103(a) over Morris et al. (EP 0 830 858 A1) as evidenced by Nakajima et al. (U.S. 3,926,817)

Claims 34-51 stand rejected as being obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. Applicants respectfully traverse.

Claim 34 recites a pharmaceutical formulation comprising a **homogeneous mixture** of: (a) **uncoated** olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof; (c) a polysaccharide and optionally; d) one or more additional excipients.

Morris teaches an olanzapine formulation in which the active ingredient olanzapine is coated by a polymer. Morris repeatedly emphasizes the criticality of coating olanzapine with a suitable polymer in many paragraphs. *See*, for example, the abstract, page 2, lines 6-28 and 45-51, page 4, lines 45-57, and claim 1.

Morris does not disclose a formulation comprising uncoated olanzapine. Morris in fact contains many statements that would discourage or teach away a person of ordinary skill in the art from making an uncoated olanzapine formulation.

At page 2, lines 32-51, Morris discloses:

> Olanzapine, a potent compound showing promising activity for use in treating psychotic patients, tends to be metastable, undergo pharmaceutically undesired discoloration, and demands care to assure homogeniety of the finished solid formulation.
>
> Applicants have discovered that olanzapine undergoes undesirable discoloration when contacted with certain excipients including powder blends. Further, the discoloration is exacerbated by ambient air conditions, at elevated temperatures, and by moist environments.
>
> Although the discoloration phenomenon does not produce an increase in the number of total related substances, the browning and mottling appearance is not generally considered pharmaceutically acceptable for commercial purposes. Further, the discoloration is particularly disturbing when a tablet formulation is administered to a psychotic patient, which patient may be especially troubled by the changing appearance of their medication.
>
> The discoloration phenomenon is particularly troublesome for a granule formulation. Such formulation inherently exposes more olanzapine to ambient or humid conditions by virtue of the increased outer surface area relative to a solid tablet formulation. The present invention provides the desired pharmaceutically elegant granule formulation.
>
> Applicants have discovered that coating the olanzapine compound with a polymer selected from . . . as a coating or subcoating provides a uniform, physical stability and effectively prevents the undesired discoloration phenomenon in the formulation.

When reading the above disclosures, a person of ordinary skill in the art would not leave olanzapine uncoated, which would result in undesirable color change and appearance, in particular considering that the olanzapine formulation would be used for a patient suffering from hallucinations, delusions, and being out of touch with reality. See MPEP 1504.03 ("A *prima facie* case of obviousness can be rebutted if the applicant...can show that the art in any material respect 'taught away' from the claimed invention...A reference may be said to teach away when a person of ordinary skill, upon reading the reference...would be led in a direction divergent from the path that was taken by the applicant." *In re Haruna*, 249 F.3d 1327, 58USPQ2d 1517 (Fed. Cir. 2001).

Nevertheless, the Examiner relies on a single paragraph at col. 4, lines 47-49 of Morris to argue that a formulation comprising uncoated olanzapine as recited in the claims of the present application would have been obvious.

Specifically, at col. 4, lines 47-49, Morris discloses: "uncoated tablets stored at ambient conditions (approximately 23^0C and 40% relative humidity) in amber, high density polyethylene bottles do not show signs of discoloration after 24 months; however if the bottle is opened such that the tablets are exposed to open air ambient conditions then discoloration **within** 5 days." (Emphasis added.). The Examiner speculates, "one of ordinary skill in the art would have indeed found it obvious to formulate uncoated tablets of olanzapine if the intended use is for rapid consumption." *See* page 3,lines 8-9 the Office Action. The Examiner's argument is flawed in several aspects.

First, it is not clear from the Morris disclosure that the "uncoated tablets" necessarily refer to a formulation comprises uncoated olanzapine. From its plain meaning, the term "uncoated tablets" probably refer to a plurality of tablets, each of which comprises olanzapine, coated or uncoated, and other excipients, and the tablets so formed is not coated. In other words, it probably means that the tablets are not coated, and does not necessarily mean that the olanzapine ingredient itself in the tablets is uncoated.

Second, uncoated tablets in no way means that the tablet composition is a homogenous mixture as recited in the claims of the present application. It is the inventors of the present application that surprisingly found: "stable pharmaceutical formulations comprising olanzapine as the active ingredient, which do not show any undesired discoloration and have an excellent dose uniformity, can be prepared by a simple direct compression process if olanzapine or a pharmaceutically acceptable salt thereof is first homogenously mixed with certain excipients and

then subjected to direct compression." *See* page 3, lines 23-26. Due to olanzapine's known moisture sensitive, metastable nature in the art, a person of ordinary skill in the art would formulate olanzapine formulation very carefully, and try to develop a pharmaceutically elegant granule formulation. *See* Morris, page 2, lines 6-10, and Chakarabarti, col. 11, Example 4. Without knowing the surprising discovery by the present inventors, a person of ordinary skill in the art would not simply mix olanzapine with other excipients evenly to make a homogenous mixture, by e.g., direct compression.

Third, the Examiner incorrectly states that, according to Morris, the uncoated tablets will only discolor after exposed to open air ambient conditions exactly **by, not before** 5 days. See page 3, line 15 to page 4, line 2 of the Office Action. This apparently violates the plain meaning of "**within** 5 days" of Morris. *See Dictionary.com Unabridged.* Retrieved March 02, 2010, from Dictionary.com website (the relevant meaning of the term "within" is: "at or to some amount or degree **not exceeding**: *within two degrees of freezing.*" Accordingly, "within 5 days" as disclosed in Morris includes any period of time that does not exceed 5 days, e.g., 1 day, 2 days, 3 days, 4 days, 1 hour, 20 minutes, and even 1 minute, after the uncoated tablets' exposure to ambient conditions. Therefore, a person of ordinary skill in the art would not formulate a composition comprising uncoated olanzapine, which according to Morris, may discolor any time, but no later than 5 days, after exposure to the ambient conditions.

Fourth, the Examiner incorrectly argued that a person of ordinary skill in the art would disregard increased manufacturing and marketing cost in connection with the use of a formulation comprising uncoated olanzapine. *See* page 3, lines 10-15 of the Office Action.

As explained in Applicants' previously submitted Amendment, if one would use uncoated olanzapine for rapid consumption, as suggested by the Examiner, s/he should at least

warn physicians and patients that the uncoated olanzapine product should be consumed as soon as possible after the package is opened. In case that the package is opened and the product is not used up immediately, the unused product will have to be abandoned due to the occurrence of discoloring. Alternatively, one may consider placing only one unit dosage of tablet(s) in an amber, high density polyethylene bottles for one-time use, which will unduly increase the manufacturing cost and be unacceptable to a manufacturer. Also, because uncoated olanzapine is so sensitive to the open air, as taught in Morris, various precautions should be adopted to make sure that the uncoated olanzapine formulation is packaged well and tight, therefore resulting in increased cost. Therefore, in view of these problems and difficulties associated with uncoated olanzapine, as suggested by Morris, a person of ordinary skill in the art would not use any uncoated olanzapine for any use, even for rapid consumption, as suggested by the Examiner.

In response, the Examiner argues that a person of ordinary skill in the art would not consider marketing or manufacture cost. Applicants disagree. It is common sense that when a person of ordinary skill in the art designs a product, this person must consider whether her or his design is practical, in particular in the pharmaceutical formulation field. Moreover, as stated above, Morris taught that coated olanzapine tablets do not have any of the problems associated with uncoated olanzapine tablets, one would use coated olanzapine tablets for normal use or "rapid consumption" as proposed and speculated by the Examiner. *See* also MPEP 2145X. D.3 ("The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986).") In other words, if there is a better, more practical solution, without any particular reason, why would a person of ordinary skill in the art formulate an impractical olanzapine formulation and then package only one dosage of olanzapine formulation in one amber, high

density polyethylene bottle for one time use?

In this aspect, MPEP2143 states:

> Note that combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art. *United States v. Adams*, 383 U.S. 39, 51-52, 148 USPQ 479, 483-84 (1966). In *Adams*, the claimed invention was to a battery with one magnesium electrode and one cuprous chloride electrode that could be stored dry and activated by the addition of plain water or salt water. Although magnesium and cuprous chloride were individually known battery components, the Court concluded that the claimed battery was nonobvious. The Court stated that "[d]espite the fact that each of the elements of the Adams battery was well known in the prior art, to combine them as did Adams required that a person reasonably skilled in the prior art must ignore" **the teaching away of the prior art that such batteries were impractical and that water-activated batteries were successful only when combined with electrolytes detrimental to the use of magnesium electrodes**. *Id.* at 42-43, 50-52, 148 USPQ at 480, 483. "When the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious."*KSR*, 550 U.S. at ___, 82 USPQ2d at 1395.

(Emphasis stated).

Sixth, the Examiner fails to properly evaluate the unexpected results of the present invention. *See* MPEP 2141 (Secondary considerations, such as unexpected results, must be evaluated under 35 U.S.C. § 103.) Although Applicants have presented this argument previously, the Examiner fails to consider it as required by MPEP2141.

Specifically, as noted above, according to the statement quoted by the Examiner from page 4, lines 45-48 of Morris, a person of ordinary skill in the art would expect that a formulation containing uncoated olanzapine would discolor any time but by not later than 5 days after the tablets are exposed to air under room temperature and 40% relative humidity. In contrast, it is Applicants, not others, who surprisingly discovered that a tablet formulation comprising a homogeneous mixture of uncoated olanzapine and other excipients in accordance with the present invention. As explained at page 3, last paragraph of the present application,

> It was surprisingly found by the present inventors that stable pharmaceutical formulations comprising olanzapine as the active ingredient, which do not show any undesired discoloration and have an excellent dose uniformity, can be prepared by a simple direct compression process if olanzapine or a pharmaceutically acceptable salt thereof is first homogeneously mixed with certain excipients and then subjected to direct compression. The direct compression is preferably performed in the absence of any solvent. In view of the fact that the excipients used by the present inventors are commonly used for manufacturing tablets, the finding that they allow the production of stable olanzapine formulations without any need for a coating or wet granulation was totally unexpected.

It is noted that at page 4, lines 3-10 of the Office Action, the Examiner states: "no discoloration would occur since Morris explicitly teaches such formulations can in fact be formulated and that no discoloration occurs for 24 months." But the Examiner fails to mention that Morris explicitly states that its uncoated tablets when exposed to open air ambient conditions will discolor within 5 days. **A person of ordinary skill in the art would by no means reasonably expect based on Morris the surprising discovery of the present invention before filing of the present application.**

Additionally, the Examiner has previously stated that the findings by WIPO do not necessarily bind USPTO's examination of the counterpart application. While Applicants do not argue that USPTO should be necessarily bound by WIPO's decision, Applicants would like to again bring to the Examiner's attention the underlying substantive reasons for WIPO's findings that the claims of the corresponding PCT application are novel and have an inventive step in view of the same prior art applied by the Examiner here, i.e., Morris et al. For example, **WIPO's specific discussion** as to why the claims are novel and have an inventive step in view of Morris certainly **sheds light on how a person of ordinary skill in the art would understand Morris, the differences between Morris and the present invention, and whether the results of the present invention would be unexpected from Morris**. Indeed, WIPO's understanding about

Morris is consistent with Applicants' above statement that Morris fails to teach a formulation comprising uncoated olanzapine and in fact teaches away from such a formulation.

Based on the foregoing, claim 34 is not obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. For at least the same reasons, none of claims 35-51, each of which depends from claim 34, is obvious under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima. Withdrawal of the rejection of claims 34-51 under 35 U.S.C. §103(a) over Morris as evidenced by Nakajima is respectfully requested.

II. Rejection of claims 34-51 as being obvious under 35 U.S.C. §103(a) over Chakrabarti et al. (U.S. 5,229,382) in view of Rubinstein et al. (Pharmaceutics: The Science of Dosage Form Design, 1988, Tablets, Chapter 18, pgs. 304-321).

Claims 34-51 stand rejected as being unpatentable over Chakrabarti in view of Rubinstein under under 35 U.S.C. §103(a). Applicants respectfully traverse.

EP054436B1, the European counterpart to Chakrabarti (a U.S. patent), has been extensively discussed in the present application. *See* pages 1-2, the bridging paragraph and pages 2-3, the bridging paragraph.

As explained in the Applicants' previously submitted Amendment, Chakrabarti fails to disclose a **homogeneous mixture** of: (a) uncoated olanzapine or a pharmaceutically acceptable salt thereof as an active ingredient; (b) a monosaccharide and/or oligosaccharide and/or a reduced or oxidized form thereof; (c) a polysaccharide and optionally; and d) one or more additional excipients, as recited in independent claim 34 of the present application. Chakrabarti merely teaches a formulation prepared by granulation and compression. *See* Example 4 of Chakrabarti.

Chakrabarti's method of granulating does not lead to a homogenous mixture of olanzapine with other excipients. As shown in Exhibit 1 (relevant pages of Remington's

Pharmaceutical Sciences, 18th edition), granulation is used to form larger size of granules from powdered material, such as active ingredient and part of the excipients, and then the granules are blended and compressed together with lubricant, such as magnesium stearate to form tablets. Therefore, the tablets made by granulation are not a homogenous mixture, because the ingredients are not evenly distributed at different position or depth of the tablets. There are two types of granulation, i.e., dry granulation (with no solvent involved) and wet granulation (with solvent involved). Wet granulation is the most widely used and most general method of tablet preparation. *See*, Exhibit 1, page 1641, right column, 3rd paragraph. Dry granulation is used when tablet ingredients are sensitive to moisture or are unable to withstand elevated temperatures. *See* Exhibit 1644, right column, 3rd full paragraph. Direct compression consists of compression tablets directly from powdered material without modifying the physical nature of the material itself.

Therefore, the tablet formulation made by granulation, as disclosed in Chakrabarti, is inherently not a homogenous mixture, even though Chakarabarti does not explicitly disclose so, as argued by the Examiner.

The Examiner also argues that Chakarabarti discloses the use of conventional techniques for the preparation of olanzapine formulation and therefore discloses a homogenous mixture of olanzapine. *See* pages 4-5, bridging paragraph. This argument lacks merit. It is noted that at col. 8, lines 16-46, Chakrabarti broadly discloses that conventional techniques may be used to prepare a formulation, which can be in the form of tablets, capsules, injection solution, suspension, suppositories, and sachets. But nowhere does Chakarabarti disclose the use of direct compression or any other method to make a homogenous mixture. As stated above, wet granulation is the most widely used conventional technique, but it cannot produce a

homogeneous mixture. Also as explained previously, due to olanzapine's known moisture sensitive, metastable nature in the art, a person of ordinary skill in the art would formulate olanzapine formulation very carefully, and try to develop a pharmaceutically elegant granule formulation, which is not a homogenous mixture. *See* Morris, page 2, lines 6-10, and Chakarabarti, col. 11, Example 4. Without knowing the surprising discovery by the present inventors, a person of ordinary skill in the art would not simply mix olanzapine with other excipients evenly to make a homogenous mixture by, e.g., direct compression.

The secondary reference Rubinstein et al discloses general methods of preparing compressed tablets, and cannot remedy the deficiency discussed above in connection with the primary reference Chakrabarti et al. Therefore, combination of Chakrabarti and Rubinstein, as proposed by the Examiner, would not lead to the formulation of claim 34. Therefore, claim 34 is not obvious under 35 U.S.C. §103(a) over Chakrabarti et al. and Rubinstein et al. For at least the same reason, none of claims 35-51, each of which depends from claim 34, is obvious under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein et al. Withdrawal of the rejection of claims 34-51 under 35 U.S.C. §103(a) over Chakrabarti and Rubinstein is respectfully requested.

Based on the foregoing, it is believed that the present application has been placed in condition of allowance. Early and favorable consideration is respectfully requested.

It is believed that no additional fees or charges are required at this time in connection with the present application. However, if any fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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